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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/857,448	MIDOUX ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 June 2001* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/28/04 has been entered.

Claims 1-19 were canceled and claims 20-35 were added as requested.

Claims 20-35 are pending and under consideration in this Office Action.

Claim Objections

Claims 20 and 35 are objected to as ungrammatical. It is suggested that the phrase "An oligomeric conjugate positively charged" should be rewritten as "A positively charged oligomeric conjugate".

Claim 24 is objected to because it recites both "imidazole" and "imidazol". Applicant should decide which spelling is desired and use that one consistently. Also, "metyl" and "limidazol" are misspelled at line 7 of the claim, and the 'i' in pteroic acid (penultimate line of claim) has two dots.

Claim 30 is objected to. It is suggested that, in the phrase "and/or in a cell nucleus", the word "into" should be substituted for the word "in".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 and dependents are indefinite because it is unclear what is meant by the term "substituted" in the context of NH_3^+ groups. For example, regarding paragraph 2 and items a) and b), the Examiner was at first under the impression that "substituted NH_3^+ " meant that one of the H atoms of NH_3^+ had been replaced by a protonable residue. However, at item c) of claim 20 it appears that "NH_3^+ of said monomers are optionally substituted by uncharged residues" refers to the replacement of the entire NH_3^+ group, as a reduction the number of positive charges in the conjugate is required as a result of substitution. As such it is unclear if Applicant intends in paragraph 2 and items a) and b) to replace only a hydrogen of NH_3^+, or to replace the entire NH_3^+, with a protonable residue. Similarly it is unclear if the molecules constituting a recognition signal in item d) are intended to be added onto NH_3^+, or to replace NH_3^+. As such the structure of the claimed molecules is unclear.

Claim 20 and dependents are indefinite because they recite said "monomeric component" without proper antecedent basis. The only antecedent for monomeric

component is "monomeric components having substituted and unsubstituted NH_3^+". It is unclear to which monomeric component "said monomeric component" refers. The phrase "said monomeric component is substituted in a ratio of at least 50%" renders the claims indefinite also. A given monomer is either substituted or it is not, it cannot be only 50% substituted. Furthermore, it is unclear if Applicant intends that the monomeric component may be substituted at any position, or whether the substitution must take place on the NH_3^+. Because it is unclear where on the monomer the substitution may take place, it is unclear which monomers are substituted and which are not, because there is no standard structure set forth for an unsubstituted monomer, i.e. there is no basis for comparison to determine what is a substituted monomer and what is not. Finally it is unclear if Applicant intends NH_3^+ to be a substituent according to items a) and b), or whether Applicant intends that a substituent according to items a) and b) must be added to, or used to replace, NH_3^+. In other words, NH_3^+ is protonated in weak acid, contains a functional group (N) allowing it to be linked to the oligomer, and as far as the Examiner knows NH_3^+ is not in and of itself recognized by a cellular receptor, so it appears to meet the criteria of a protonable residue under items a) and b). However, it is unclear if this is what Applicant intended.

Claim 20 and dependents, and claim 35, are indefinite because the metes and bounds of "protonable residues" that "are not recognized as a recognition signal recognized by a cellular membrane receptor" are unclear. It is unclear what is intended by "a recognition signal". Does Applicant wish to exclude all protonable residues

capable of a binding interaction with a cellular membrane receptor, or only those that would cause the receptor to execute its function, e.g. transduce a signal across a membrane?

Claim 20 and dependents are indefinite because they recite "the NH_3^+ of said monomers" without antecedent basis. One of skill in the art cannot know if Applicant means the substituted or unsubstituted NH_3^+ as referred to in the second paragraph of claim 20.

Claim 20 recites "the NH_3^+" without proper antecedent basis at item d) paragraph 2. Even if one assumes that "the NH_3^+" excludes substituted "the NH_3^+, and it is not clear that it does, one cannot know if the antecedent is the unsubstituted NH_3^+ recited in paragraph 2, or the unsubstituted NH_3^+ recited in item b).

Claim 20 is confusing at paragraph 5 of item d) wherein it is indicated tat a molecule containing a recognition signal may be added "by substitution of the NH_3^+ (if it is present) of said protonable residues". It is not clear what is the antecedent for "the NH_3^+". If the antecedent is the "at least one unsubstituted NH_3^+" group in paragraph 4 of item b), then the claim is confusing because it requires that this NH_3^+ must be unsubstituted, but then makes provisions for substituting it. On the other hand, if "at least one unsubstituted NH_3^+" is not the antecedent for "the NH_3^+", then "the NH_3^+" lacks antecedent basis altogether. Further, the phrase "(if it is present)" is confusing because, if the antecedent for "the NH_3^+" is "at least one unsubstituted NH_3^+" group in

paragraph 4 of item b)", then the claim requires the presence of an NH_3^+, so the meaning of "(if it is present)" is totally unclear.

Claim 25 and dependents are indefinite because it is unclear to what the terminal CO2 is bonded. The depicted bond is not attached to anything, so the structure of the claimed composition is undefined.

Claim 25 and dependents are unclear because, although they define what 'R' represents when 100% of all 'R' groups are selected from the Markush group bridging pages 5 and 6 of the amendment, they do not meaningfully not define R for situations in which less than 100% of the 'R' groups are selected from that group. For example, at page 6 of the amendment, claim 25 requires that "0-50% of all R groups (corresponding to f wherein: $0 < f \leq u$)" must be NH_3^+ or substituted NH. However, it is unclear what is the numerical value of f. The claim embraces indefinite embodiments such as when 50% of all R groups are selected from the Markush group bridging pages 5 and 6 of the amendment, and less than 50% of the R groups are selected from the Markush group bridging pages 6 and 7 of the amendment. In these situations, some fraction of the R groups remain undefined.

Claim 25 and dependents are indefinite because all recited equations involving the quantity 'u' are invalid. The claims require that $u \geq i/2$. This sets a lower limit on the value of u, but sets no upper limit, thus the numerical value of u can increase infinitely, and far beyond the value of 'i'. So for example, the expression "i = u + j + k + h", at page 8 of the amendment, is invalid because 'u' can be greater than 'i', but the claim

does not allow for negative values of j, k, and h. The expression NH_3^+ = m =p + j + 1 is also invalid because 'p' is defined in terms of 'u', and 'u' is indefinite. Alternatively, if one interprets m as simply the total number of NH_3^+, then the expression still fails to make sense because it requires addition of the number of alpha NH_3^+ (p) to the number of omega NH_3^+ (j), and then addition of the number '1'. It is unclear to the Examiner that there is any type of NH_3^+ in the claimed structure other than an alpha or omega NH_3^+, so it is unclear how the total NH_3^+ can be the sum of alpha and omega NH_3^+ plus 1. Further, the claims define m identically to u, i.e. $m \geq i/2$. Thus the numerical value of m must be at least half of 'i' but can increase infinitely beyond 'i'. The claims do not account for values of p and j that can be summed to give numbers that are very much larger than 'i', and certainly not infinitely larger. The expression NH_3^+ = j + f-(k + h) is invalid for the reasons stated in the previous paragraph, i.e. 'f' is inadequately defined. The claim states that f may be equal to u, and u may be infinite, so clearly the expression is invalid.

Claim 27 is confusing because R is defined twice in each member of the Markush group, first as a specific chemical formula, and then as a broader generic formula. As a result it is unclear to what Applicant wishes to limit the claim, i.e. to the species or the genuses. Also, each member of the Markush group is defined in part as:

"i = [integer] n =[integer] (u) R = [structure]".

It is unclear what is the purpose of "(u)" in this definition, so the claims are confusing.

The Examiner is gets the impression that Applicant may wish to claim a composition comprising a certain number of groups R, wherein at least half of the groups R are selected from a certain set of structures. The total number of groups R from this set of structures that is present in the composition is the quantity 'u'. The remainder of the groups R are selected from a different set of structures. The total number of groups R from this set of structures that is present in the composition is the quantity 'f', such that the total number of groups R in the composition = u + f. If this impression is correct, then Applicant should amend the claims to make this clear.

Claim 27 is also indefinite because it is unclear what is intended by the expressions "(f) R = [formula]". The Examiner guesses that this is meant to limit the nature the Rf groups. Inasmuch as possible, Applicant should attempt to clearly and unambiguously point out with particularity in English the subject matter that is claimed as the invention, in accordance with the statute.

The phrase "corresponding to a number" which appears in claims 26 and dependents, renders these claims indefinite because the nature of the correspondence is unclear. If, for example, Applicant wishes that the number of R groups in a composition should be equal to a quantity 'u', then Applicant should make this clear.

Claims 28-32 are indefinite because it is unclear to which oligomeric conjugate they refer. This is because these claims refer to "an oligomeric conjugate of claim 20", rather than to "the oligomeric conjugate of claim 20." As a result, one cannot know which conjugates of claim 20 are embraced by these claims. Use of a definite article

would make it clear that the dependent claims embrace all of the conjugates of claim 20.

Claim 29 is indefinite because it recites "said biological molecules" without antecedent basis.

Claims 30-32 are indefinite because the recited method steps are not concordant with the purpose set forth in the preamble. These claims are methods of intracellular transfer of oligonucleotides, but they recite no end point showing that the method is accomplished.

Claim 35 is indefinite because it is unclear what constitutes the recited ratio of "at least 50%. The claim fails to describe to what the amount of free NH_3^+ is being compared. It is also unclear what is the purpose or meaning of the phrase "protonable residues" in item a) of the claim. Also, as in claim 20 and dependents, it is unclear as to whether the claim requires free, unsubstituted NH_3^+ or not. On the one hand, in item a) the claim requires "a ratio of at least 50%" of free NH_3^+, but on the other hand in item c) the claim stipulates that the free NH_3^+ may be substituted. As a result it appears that the oligomer need have no free NH_3^+ as all as long as the oligomer is positively charged.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 20-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 20-35 are drawn to the genus of "protonable residues not recognized as a recognition signal recognized by a cellular membrane receptor". The specification fails to identify a single member of this genus. While the specification teaches that such classes of molecules as imidazoles, quinolines, pterines, and pyridines represent species of this genus, a search of the art indicates otherwise. For example, Chen et al (Plant Physiol. 115(3): 1127-1134, 1997) taught that the imidazole histidine, exemplified in claim 27, is specifically bound by a membrane protein. See abstract. Hershfield et al (J. Biol. Chem. 251(17) 5141-5181, 1976) taught that a series of pyridine derivatives served as competitive and noncompetitive inhibitors of glucose membrane transporters, noting that the best inhibitors bound about 100-fold more tightly than glucose itself. See abstract. Doyle et al (Pharm. Rev. 55(1) : 105-131, 2003) taught that quinolines act to open potassium ATP channels, and Vezmar et al (Biochem. Pharmacol. 56(6): 733-742, 1998) taught that the multidrug resistance protein binds a quinoline-based drug. See abstracts. Finally, Huennekens et al (Adv. Enz. Reg. 20: 389-408, 1982) taught

that leukemia cells bind and transport a variety of pterins. See abstract. As such it is clear that the classes of molecules contemplated by Applicant as not being recognized by cellular receptors are in fact recognized by such receptors.

It is noted that Applicant need not reduce the invention to practice or drawings in order to adequately describe it, as long as a representative number of species are described by relevant identifying characteristics such as a known or discloses correlation between structure and function. However, in this case, such a description would not be possible due to the overwhelming array of different membrane receptors and ligands. As such, in the absence of the description of a single member of the claimed genus by reduction to practice or relevant identifying characteristics, one of skill in the art could not conclude that Applicant was in possession of the claimed genus at the time the invention was filed.

Claims 20-24, and 29-35 are drawn to oligomers with a polymerization degree of from 5-36. The claims recite further limitations including the need for at least 50% of the monomers to comprise a substituted or unsubstituted NH_3^+, but the specification provides little further description of the backbone of the oligomer. At pages 9 and 12 the specification teaches that the backbone of the oligomer can be a hydrocarbon chain comprising peptide bonds with as many as 21 backbone carbons between each peptide bond. However, the genus of polymers that are embraced by the instant claims is far broader than this description, such that the claims as written do not provide a substantially essential structure for the backbone of the oligomer. As discussed above,

in order to satisfy the written description requirement, one must describe a representative number of species of the claimed genus, either by reduction to practice, drawings or description of relevant identifying characteristics. In this case, the specification has described only certain polymers structures comprising peptide bonds separated by between 1-21 saturated carbons. As such, one of skill in the art could not conclude that Applicant was in possession of the entire claimed genus at the time of the invention. The specification and the state of the prior art of record provide sufficient description of polymeric complexes comprising the oligomers with the formulas set forth in pages 9 and 12, wherein B is an imidazole, pterine, quinoline, or pyridine.

With respect to claims readable on a genus of oligomers formed from monomers having free NH3+ groups which must exhibit a biological function of being able to function as a conjugate to other disclosed functional groups, *e.g.,* nucleic acid molecules, residues comprising a weak base and an NH3+, and cellular recognition signals, and to function as a whole as a nucleic acid or peptide transfer vector, the specification only provides sufficient description of the oligomers with the formula as set forth in claims 25 and 26.

With respect to claims readable on a genus of unspecified residues that must exhibit a biological function of being protonated in a weakly acid medium and causing destabilization of cell membrane, said unspecified residues also carrying an unspecified functional group that must exhibit a biological function of not being active with recognition signal recognized by a cell membrane receptor, the specification only

provides sufficient description of a oligomers having a backbone of the formula as set forth in claims 25 and 26, and comprising residues having an imidazole, pterine, quinoline, or pyridine, and an NH3+ functional group, and residues having the formulae as set forth on pages 7 and 8 of the as-filed specification

With respect to claims readable on a genus of cellular recognition signals, the specification only provides sufficient description of cellular recognition signals which are peptide based recognition signal sequence, oligosaccharide based recognition signal or monosaccharide based recognition signal.

In other words, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or assays for making the polymer genus as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of oligomeric conjugates and/or functional groups thereof that must exhibit the disclosed biological functions as contemplated by the as-filed specification.

It is not sufficient to support the present claimed invention by disclosing oligomeric complexes comprising the oligomer with the formula as set forth in claims 25 and 26, wherein B is a residue with an imidazole nucleus, or a compound having the formulae as set forth on pages 6 and 7 of the as-filed specification, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any and/or all other oligomeric conjugates having other residues with the biological functions

as contemplated by the specification and the claims. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of Applicant's effective filing date. Claiming all oligomeric conjugates and/or functional groups and/or recognition signals that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of the claimed oligomeric complexes that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, In view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Enablement

Claims 20-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, since the claimed invention is not supported by a sufficient written description for possessing of the genus of oligomeric complexes as recited in the claims, particularly in view of the reasons set forth above, one skilled in the art would not known how to use and make the claimed invention so that it would operate as intended, *e.g.* functions as a nucleic acid delivery vector that exhibits all of the biological functions as recited in the claimed invention.

For example, as discussed above, the specification fails to identify a single member of the genus of "protonable residues not recognized as a recognition signal recognized by a cellular membrane receptor" even though these protonable residues are required by the claims. While Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the identification of the required protonable residues cannot be overlooked as a trivial omission in the process of providing an enabling disclosure. Instead, these residues are a critical element of the claims. Because Applicant has failed to describe such residues, or to provide guidance as to how to make them, one of skill in the art would have to invent or discover them in order to make the claimed invention. Such experimentation is undue in the absence of guidance, description, or working examples.

Claim 33 is directed to a pharmaceutical composition comprising as an active substance an oligomeric conjugate according to claim 20. As discussed above under 35 USC 112, second paragraph rejections, claim 20 is indefinite because it is unclear to what the oligomer of claim 20 is conjugated. MPEP 2164.01(c) states:

> When a compound or composition is limited by a particular use, enablement of that claim should be evaluated based on that use.

In this case, enablement of the claimed composition and method must be evaluated in terms of the use of the composition as a pharmaceutical. The

specification fails to define the term "pharmaceutical", so in order to understand how this term limits the invention, one must determine its accepted meaning in the art. According to Steadman's Medical Dictionary (26th Edition, 1995) "pharmaceutical" means "relating to pharmacy or to pharmaceutics". In the same dictionary, "pharmacy" is defined as a "practice that emphasizes the therapeutic use of drugs rather than the preparation and dispensing of drugs." Finally, Steadman's Medical Dictionary defines "drug" as a "therapeutic agent; any substance, other than food, used in the prevention, diagnosis, alleviation, treatment, or cure of disease in man and animal." Thus, to enable a pharmaceutical use for the claimed composition, the specification must teach how to use the substance, without undue experimentation, for the prevention, diagnosis, alleviation, treatment, or cure a disease in the animal to which the substance is administered. Because the claim requires that the oligomeric conjugate itself is an active substance, the claim clearly embraces conjugates that are intended to cause a pharmacological effect, in and of themselves.

The specification teaches the use of the claimed conjugates to deliver to cells biologically active substances such as oligonucleotides and peptides. However, the specification fails to teach how to use the claimed conjugates themselves, in the absence of e.g. oligonucleotides or peptides, to achieve any therapeutic or diagnostic effect. In other words, in light of the teachings of the specification one of skill in the art would consider the claimed conjugates to be delivery molecules that do not act as therapeutic or diagnostic active agents, but function instead in the delivery of such

agents. As discussed above, while Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In this case, the claim identifies the oligomeric conjugate as an active substance in a pharmaceutical composition, thus guidance as to how to use the claimed conjugate itself as a therapeutic or diagnostic agent cannot be considered a minor detail which can be omitted in the process of providing an enabling disclosure. In the absence of such guidance, one of skill in the art would have to discover or invent means of using the invention as intended in the claim. Such experimentation is undue. This portion of the rejection can be overcome by deleting the term "pharmaceutical".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 20-26 and 33-35 rejected under 35 U.S.C. 103(a) as being unpatentable over Midoux et al (WO 98/22610, published 5/28/98).

WO 98/22610 was filed as PCT/FR97/02022 and is the priority document for US Patent 6,372,499. The contents of WO 98/22610 will be discussed by reference to this

English language version. Midoux teaches oligomers with a polymerization degree as low as 15, in which at least 10% of the monomers have free NH3+ groups substituted by residues that are protonable in a weak acid medium, such as histidines, pterines, quinolines, or pyridines, leading to destabilization of cell membranes. See entire document, e.g. abstract; column 4, lines 20-24; column 4, line 55 to column 5, line 40; column 6, line 48 to column 8, line 43; and column 10, line 44 to column 11, line 38. It is noted that the instant claims require at least 50% substitution. However, the recited "at least 10%" in the cited art is reasonably interpreted as embracing 10% to 100%, so the instantly claimed "at least 50%" is embraced by the range in the cited art. As such it would have been obvious to one of ordinary skill in the art to arrive at the claimed conditions through the process of routine optimization within the range in the cited art. Note that the instant application shows that the instnat invention functions to deliver polynucleotides when the level of substitution is 53%. See Table 1 on page 39.

Thus the invention as a whole was prima facie obvious.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 20-26 and 33-35 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, and 10-15 of U.S. Patent No. 6,372,499. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-6 and 10-15 of '499 teach species of the instantly claimed genuses. As discussed above, '499 teaches at least 10% substitution of the oligomer NH3+ groups, and does not exclude substitution of 50% or greater of these groups (except in claims 7-9 which were not relied upon in this rejection). As such, the cited art clearly embraces 10% to 100% substitution, thereby rendering the instant claims obvious. See entire document, e.g. abstract; column 4, lines 20-24; column 4, line 55 to column 5, line 40; column 6, line 48 to column 8, line 43; and column 10, line 44 to column 11, line 38. It would have been obvious to one of ordinary skill in the art at the time of the invention to arrive at the instantly claimed degree of substitution through routine optimization within the range disclosed by Midoux.

Conclusion

No claim is allowed. Claims 27-32 appear to be free of the prior art of record, however, due to the indefiniteness of the claims, a complete search of the prior art was not possible.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 571-272-0564.

Richard Schnizer, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER